REMARKS

After entry of the foregoing amendments, Claims 1-52 are cancelled without prejudice. Further, new Claims 67-114 have been added and Claims 53, 55 and 60-64 have been amended. Therefore, by the foregoing amendments, Claims 53-114 are pending for examination. The new and amended claims are supported by the specification and the claims as originally filed. No new matter has been added. The specific changes to the amended claims are shown above with the insertions being underlined and the ~~deletions shown stricken through~~.

Applicants respond below to the specific rejections and objections raised by the Examiner in the Office Action of January 30, 2003.

Discussion of Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-66 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office Action alleges that Claims 1-66 are not clear due to recitation of the term "adapter sequences," which according to the Office Action is vague and raises questions as to Applicants actually intend the term to mean. The Office Action also rejects Claim 14 as lacking proper Markush format.

As set forth above, Claims 1-52 have been cancelled and new Claims 67-114 have been added. Also, the other claims using the term "adapter sequence" have been amended. Applicants respectfully assert that the new Claims 67-114 and Claims 53-66 as amended are supported by the application as filed, and that the claims are clear and definite.

Claim 14 has been amended as shown above. Amended Claim 14 is written in Markush format, and is therefore, clear and definite.

In view of the above comments, reconsideration and withdrawal of the § 112, second paragraph rejections is respectfully requested.

Discussion of Rejections under 35 U.S.C. § 102

Claims 1-9, 13-14, 16-21, 26-27, 29-48, 53-54 and 64-66 were rejected under 35 U.S.C. § 102(b) as being anticipated by Zhang et al., Nature Genetics 20:123-128 (1998) (referred to hereafter as "Zhang"). Also, Claims 1, 7-8, 13-14, 16-17, 29-31, 35-37 and 41-44 were rejected

under § 102(b) as being anticipated by Bradshaw et al., Nucleic Acids Research 23(23):4850-4856 (1995) (referred to hereafter as "Bradshaw").

Zhang and Bradshaw do not anticipate the above listed claims. To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. ... There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

Zhang

According to the Office Action, Zhang teaches a method of homologous recombination using linear DNA carrying the Tn5 kanamycin resistance gene, neo, made by PCR methods. The Office Action also states that Zhang teaches that the DNA constructs have homology arms of particular lengths, that the construct and fragment are cotransformed into *E. coli*, and that the products include a selectable gene. Also, according to the Office Action, Zhang teaches a cassette made using PCR, which cassette disrupted a LacZ gene and a construct that subsequently repaired the LacZ gene.

Zhang does not anticipate new independent Claim 67, and the claims depending therefrom, because Zhang does not teach each and every element of these claims. For example, Zhang does not disclose cloning a nucleic acid fragment into a linear vector. The vector disclosed in Zhang is a circular plasmid. Given the significant structural and functional differences between circular vectors and linear vectors, and given that Zhang does not disclose the use of the linear or linearized vectors, Zhang does not anticipate new Claim 67. For similar reasons, Zhang does not anticipate amended independent Claim 64 reciting a kit which comprises a linear vector.

Zhang also does not anticipate independent amended Claim 53 because, *inter alia*, it does not disclose a vector that has a dysfunctional selection marker lacking a critical element and a nucleic acid insert that contains the critical element. According to the Office Action Zhang teaches a cassette made using PCR that disrupted the lacZ gene of the plasmid. The Office

Action further alleges that Zhang teaches a fragment having an intact lacZ gene which upon recombination repaired the lacZ gene.

Referring to Figure 4 of Zhang, the plasmid either has no selection marker or only has a functional selection marker. However, Claim 53 recites "wherein the vector has a dysfunctional selection marker lacking a critical element and said nucleic acid fragment contains said critical element." Exemplary explanation of dysfunctional selection marker and a critical element is set forth in the specification at pages 12 line 19 bridging page 13 line 3:

> Examples of a dysfunctional selection marker include an incomplete sequence of a resistance gene . . . Additional examples include reporter genes, such as the lacZ gene, and the like. . . . Other dysfunctional selection markers can include genes encoding products necessary for a metabolic or cellular pathway, and the like.
>
> The incomplete sequence, lacking a critical element, is completed by insertion of the lacked sequence or critical element upon a successful homologous recombination. In some embodiments the incomplete sequence can be missing at least a portion of a protein coding region, or, e.g., all or part of a regulatory element such as a promoter or termination sequence. The missing portion can be a major portion of the critical element or selection marker, or only a minor portion (e.g., one or more critical nucleotide residues).

Zhang does not disclose methods where a vector has a dysfunctional selection marker and where a critical element is supplied to the vector by the nucleic acid insert because Zhang either provides plasmid with no selection marker at all (functional or dysfunctional), or has a functional selection marker. Thus, Zhang does not teach each and every element of Claim 53.

Therefore Zhang does not anticipate new Claims 67-114, or Claims 53-54 and 64-66 as amended, because it does not teach each and every element of the claims.

Bradshaw

According to the Office Action, Bradshaw teaches a method of homologous recombination using the plasmid pClasper that includes two linker sequences that can be either 20 or 40 base pairs in length, and that the plasmid includes a selection element, such as chloramphenicol.

Bradshaw does not anticipate new Claims 67 or any of the claims depending therefrom, because Bradshaw does not teach each and every element of Claim 67. For example, Bradshaw

does not disclose cloning methods using homologous recombination in a bacterial cell. The method of homologous recombination disclosed by Bradshaw is a yeast based method and therefore incorporation of the fragment into the vector by homologous recombination does not occur in a bacterial host cell as required by Claim 67.

Furthermore, Bradshaw does not disclose incorporating flanking sequences onto the *nucleic acid fragment* by PCR. Incorporation onto the nucleic acid fragment rather than onto the vector, permits, for example, the use of the same vector for the cloning of any nucleic acid fragment. A flanking sequence (comprising a homology sequence homologous to sequence on the vector) easily can be added to any nucleic acid fragment. In contrast, Bradshaw discloses a method in which recombinogenic ends of about 500 base pairs are added to *the vector*. Thus, a new vector with 500 base pair homology sequences must be generated in order to clone every new nucleic acid fragment. Because Bradshaw discloses a yeast based system and one in which the adapter sequence is added to the vector rather than to the nucleic acid fragment, Bradshaw does not anticipate Claim 67 or any claims depending therefrom.

In view of the foregoing, Applicants request that the Examiner reconsider and withdraw the rejections based on 35 U.S.C. § 102.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. Any claim amendments, which are not specifically discussed in the above remarks, are made in order to improve the cosmetics of the claims. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 27, 2003

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